ORIGINAL ARTICLE

Vasopressors or Fluids in Early Septic Shock

The ARISE FLUIDS Investigators, the ANZICS Clinical Trials Group, and the ACEM Clinical Trials Network

ABSTRACT

BACKGROUND

The optimal approach to early resuscitation in septic shock is unknown. Equipoise exists between the use of larger volumes of intravenous fluids to restore perfusion and the use of early vasopressor therapy along with smaller volumes of fluids to minimize potential harm from excess fluid.

METHODS

We randomly assigned adult patients who presented to the emergency department with septic shock to receive either fluids at restricted volumes and early vasopressor therapy (vasopressor group) or higher volumes of fluids and later vasopressor therapy (fluids group) for at least 6 hours and up to 24 hours. The primary outcome was days alive and out of the hospital from randomization to day 90.

RESULTS

A total of 1000 patients underwent randomization, with 499 assigned to the vasopressor group and 501 to the fluids group. Informed consent was not obtained for 37 patients, which left 963 patients in the intention-to-treat population (481 in the vasopressor group and 482 in the fluids group). Three patients in the fluids group were lost to follow-up for the primary outcome. In the first 24 hours after randomization, patients in the vasopressor group received less intravenous fluid than those in the fluids group (median difference, –1108 ml; 95% confidence interval [CI], –1395 to –850). The percentage of patients who received vasopressors was higher by 18.9 percentage points (95% CI, 13.3 to 24.5) in the vasopressor group. The median number of days alive and out of the hospital at day 90 was 76 (interquartile range, 55 to 83) in the vasopressor group and 76 (interquartile range, 55 to 82) in the fluids group (difference, 0.0 days; 95% CI, –2.7 to 2.7; P=1.00). Adverse events occurred in similar percentages of patients in the two groups, except for pulmonary edema (0.6% in the vasopressor group vs. 5.0% in the fluids group; P<0.001).

CONCLUSIONS

Among adult patients who presented to the emergency department with septic shock, an approach that involved restricted fluid volume and early vasopressors did not result in a greater number of days alive and out of the hospital at day 90 than an approach involving greater fluid volume and later administration of vasopressors. (Funded by the Australian National Health and Medical Council Medical Research Future Fund and the New Zealand Health Research Council; ARISE FLUIDS ClinicalTrials.gov number, NCT04569942.)

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*A complete list of committee members, participating sites, and investigators in the ARISE FLUIDS trial is provided in the Supplementary Appendix, available at NEJM.org. The Australasian Resuscitation in Sepsis Evaluation: Fluid or Vasopressors in Emergency Department Sepsis (ARISE FLUIDS) trial is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), the Australasian College for Emergency Medicine Clinical Trials Network (ACEM CTN), and the Australian and New Zealand Intensive Care Research Centre (ANZIC RC).

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The optimal approach to intravenous fluid volume and timing of vasopressor initiation in patients with early septic shock is unknown.[1,2] In patients with sepsis-induced hypotension, the Surviving Sepsis Campaign guidelines provide a weak recommendation for intravenous fluids administered at a dose of at least 30 ml per kilogram of body weight within the first 3 hours after recognition of the hypotension.[3] The European Society of Intensive Care Medicine guidelines make a similar recommendation and call for randomized trials to assess the initial fluid dose and subsequent administration during the optimization phase (typically the first 24 hours).[4] Neither guideline makes specific recommendations regarding the timing of vasopressor initiation. Vasopressors are typically administered in the intensive care unit (ICU), and the use of these agents to support a restricted fluid strategy may increase demand for beds and contribute to inequities when ICU resources are constrained.[5] Limited evidence to guide early resuscitation contributes to practice variation in the management of septic shock.[6] Clinical uncertainty is compounded by reports of potential adverse effects that occur with excess fluid administration.[7]

The largest randomized trial to evaluate a restrictive fluid strategy for early septic shock was stopped for futility and showed no benefit with regard to mortality.[8] Although two subsequent meta-analyses of trials involving patients with septic shock in the emergency department and ICU showed that lower fluid volumes do not reduce mortality, imprecise treatment-effect estimates do not rule out clinically important benefit or harm.[9,10] Findings in small, single-center trials suggest benefit with early vasopressor initiation; however, more evidence is needed to inform the management of early septic shock.[11-13]

We conducted the Australasian Resuscitation in Sepsis Evaluation: Fluid or Vasopressors in Emergency Department Sepsis (ARISE FLUIDS) trial to test whether a strategy of restricted fluid volume and early vasopressors, as compared with a strategy of greater fluid volume and later vasopressors, would increase the number of days alive and out of the hospital at day 90 among adult patients who presented to the emergency department with early septic shock.

Methods

Trial Design and Oversight

We conducted an investigator-initiated, multicenter, open-label, randomized trial at 51 sites across three countries (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was designed and conducted by the trial management committee (listed in the Supplementary Appendix) and was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Australasian College for Emergency Medicine Clinical Trials Network. The protocol and statistical analysis plan (both available at NEJM.org) were published before enrollment was completed.[14,15]

The regulatory sponsor was Monash University, Melbourne, Australia, and the Australian and New Zealand Intensive Care Research Centre was responsible for overall coordination of the trial. The Medical Research Institute of New Zealand, Wellington, New Zealand, was the New Zealand coordinator. Ethics approval was provided by local and national institutional review boards. An opt-out or consent-to-continue model was used for enrollment in adherence with jurisdictional requirements (see the Supplementary Appendix). An independent data and safety monitoring committee provided trial oversight and reviewed an interim analysis using primary outcome data from the first 500 patients. Data were entered into an encrypted database by the site investigators. Monitoring and source-data verification were conducted according to a prespecified plan. The authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. The initial draft manuscript was written by the first author, and all the authors approved the final draft manuscript for submission. No commercial support was provided for the trial.

Patients

Adults with a clinically suspected infection were eligible if they had systolic blood pressure of less than 90 mm Hg or mean arterial pressure of less than 65 mm Hg despite receiving at least 1000 ml of fluid in the form of bolus doses (including fluids administered before hospital presentation; a bolus dose was defined as 500 to 1000 ml of fluid administered over a period of 60 minutes

or less), had a blood lactate level higher than 2.0 mmol per liter, and had begun receiving treatment with an intravenous antimicrobial agent. Key exclusion criteria were receipt of more than 2000 ml of intravenous fluids, elapse of more than 6 hours since presentation to the emergency department, and the presence of barriers to the intervention, including care limitations, immediate surgery, and clinician-determined unsuitability. A full list of eligibility criteria is provided in the Supplementary Appendix.

RANDOMIZATION AND INTERVENTIONS

We performed randomization in a 1:1 ratio using permuted blocks with variable size stratified according to site by means of a secure website that was available 24 hours a day. Eligible patients were assigned to receive restricted fluids and earlier vasopressors (vasopressor group) or greater volumes of fluid and later vasopressors (fluids group). The intervention was delivered for a minimum of 6 hours and up to 24 hours in a critical care area (emergency department or ICU). Postrandomization treatment was administered in an unblinded manner. Usual care was delivered after cessation of the trial intervention.

For patients in the vasopressor group, intravenous fluid resuscitation ceased after randomization and vasopressor therapy commenced (Fig. 1). Vasopressor type, route, dose adjustment, and target mean arterial pressure were according to clinician preference. Fluid boluses of 250 ml were permitted if indicated, including for refractory hypotension, persistent hypoperfusion (e.g., delayed capillary refill time), a lactate level higher than 4 mmol per liter or rising from the previous level despite resuscitation for 2 hours or more, persistent tachycardia, and oliguria marked by a urine output of less than 0.5 ml per kilogram of body weight per hour for 2 hours or more. Maintenance fluids were discouraged.

For patients in the fluids group, an initial intravenous fluid bolus of up to 1000 ml infused within 60 minutes was administered after randomization. Additional 500-ml boluses were administered for persistent hypotension or hypoperfusion. Unless contraindicated, administration of fluids at a dose of 30 ml per kilogram within 3 hours after presentation to the emergency department was recommended.[3] Fluid type, methods of assessing fluid responsiveness, maintenance fluids, and target mean arterial pressure were determined according to clinician preference. Treatment with vasopressors was initiated if the target mean arterial pressure was not achieved and the clinician determined that the fluid level was restored or that the patient's arterial pressure was not responsive to fluid resuscitation. In patients in the fluids group receiving vasopressors at the time of randomization, vasopressor doses were adjusted according to clinician judgment. Prespecified discontinuation was not mandated.

For patients in either group who had critical hypotension, resuscitation could include concurrent fluids and vasopressors. Patients were reassessed hourly for 6 hours and thereafter as appropriate. Regular monitoring ensured sustained adherence to trial intervention (see the Supplementary Appendix). The use of ancillary interventions, including source control and antimicrobial agents, was at the clinician's discretion.

OUTCOMES

The primary outcome was days alive and out of the hospital from randomization to follow-up at day 90.[16] We defined days alive and out of the hospital as the number of days the patient was not in an acute care hospital during the index hospitalization or during a subsequent overnight readmission to an acute care hospital. Patients who died within 90 days after randomization were assigned 0 days alive and out of the hospital. Secondary outcomes were mortality at 28 and 90 days, survival time from randomization at 90 days, days alive and at home at 90 days, and days alive and free from organ support at 28 days. Tertiary outcomes included times to discharge from the emergency department, ICU, and hospital; in-hospital mortality; and the incidence and time to first cessation of organ support. Prespecified safety outcomes included complications associated with peripheral vasopressors, pulmonary edema, and organ ischemia. Outcome definitions and details of safety reporting are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of the Australasian Resuscitation in Sepsis Evaluation trial, in which the mean (±SD) days alive and out of the hospital at day 90 under usual care was 60±31 days.[17] We calculated that enrollment of 1000 patients would provide the trial with 90% power to detect an absolute difference of 7 days

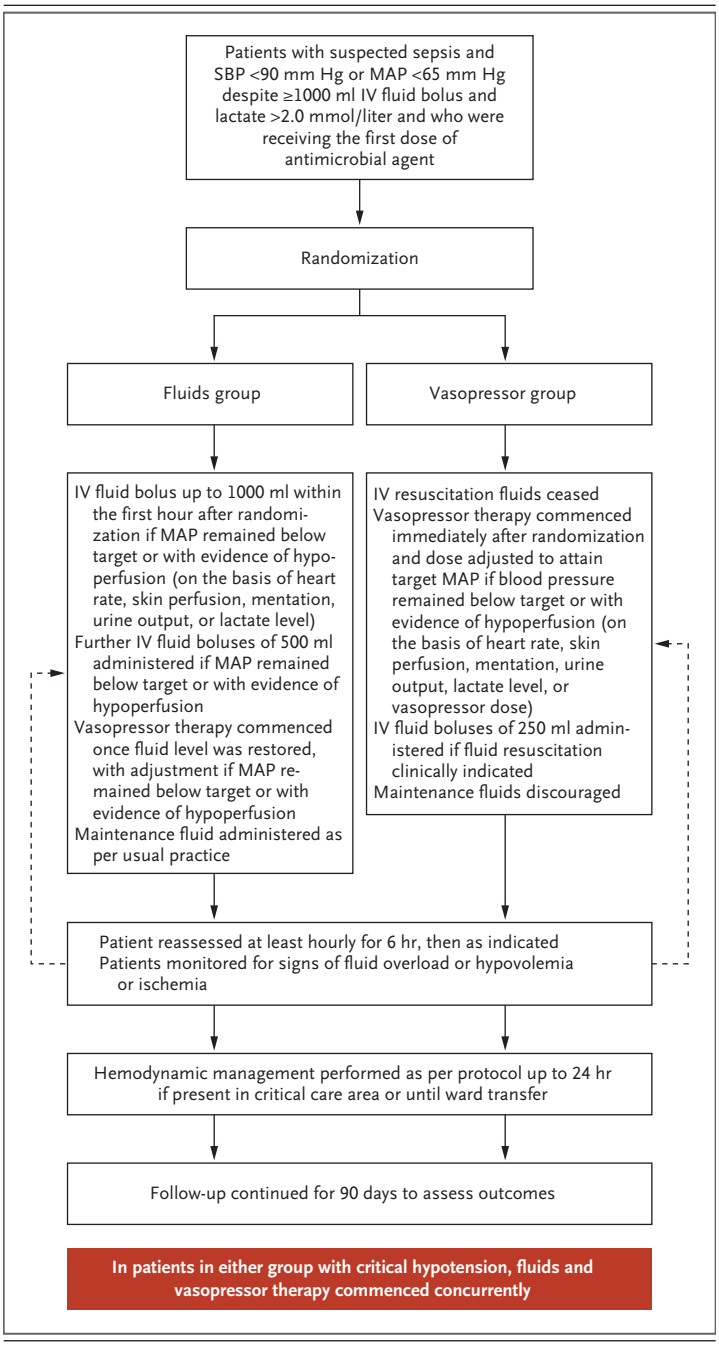


Figure 1. Trial Algorithm.

Patients with suspected septic shock who met eligibility criteria were randomly assigned to receive restricted fluids and early vasopressors or more liberal fluids and later vasopressors, as needed. The intervention was delivered for at least 6 hours and up to 24 hours while the patient remained in a critical care area (emergency department or intensive care unit). The target mean arterial pressure (MAP) was at the treating clinician's discretion for patients in both the fluids group and the vasopressor group. For patients in the vasopressor group, 250-ml fluid boluses were permitted if indicated, including for refractory hypotension, persistent hypoperfusion (e.g., delayed capillary refill time), a lactate level that was greater than 4 mmol per liter or that was increasing from the previous level despite resuscitation for at least 2 hours, persistent tachycardia, and urine output of less than 0.5 ml per kilogram of body weight per hour for at least 2 hours (oliguria). For patients in the fluids group who were receiving a vasopressor infusion at the time of randomization, protocolized discontinuation was not mandated and vasopressor doses were adjusted on the basis of clinician judgment. Additional details of the trial intervention are provided in the Supplementary Appendix. IV denotes intravenous and SBP systolic blood pressure.

in days alive and out of the hospital at day 90, allowing for 15% inflation factor for nonparametric distribution of the primary outcome event and 5% loss to follow-up. Analyses were conducted according to the prespecified statistical analysis plan and intention-to-treat principle, with patients assessed according to their assigned group. Patients who withdrew consent for use of all data were excluded.[14]

Between-group differences in median number of days alive and out of the hospital were estimated with the use of quantile mixed-effects regression (0.5 quantile), with treatment group as a fixed effect and site as a random effect. A prespecified secondary analysis was adjusted for baseline differences in the Acute Physiology and Chronic Health Evaluation (APACHE) II scores (ranging from 0 to 71, with higher scores indicating an increased risk of death),[18] infection site, country, and baseline lactate level. In a sensitivity analysis, patients who died before day 90 were considered to have had –1 day alive and out of the hospital. For patients with missing primary outcome data owing to loss to follow-up, multiple imputation was performed under a missing-at-random assumption.

Prespecified subgroup analyses for days alive and out of the hospital at day 90 were conducted for age (<65 years or ≥65 years), sex (male or female), baseline lactate level (<3 mmol per liter or ≥3 mmol per liter), APACHE II score (<15 or ≥15), infection source (respiratory, urinary, or other), and fluid volume dichotomized at the median prerandomization value, with interaction terms included in the primary model. Binary outcomes were analyzed with generalized linear mixed models, with log link to estimate relative risks and

site as a random effect. Time-to-event outcomes were analyzed with Cox mixed-effects models, with treatment group as a fixed effect and site as a random effect. Organ-support–free days were analyzed with quantile mixed-effects regression models analogous to the primary analysis.

A two-sided P value of 0.05 was considered to indicate statistical significance. Confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. Subgroup and secondary analyses were considered to be exploratory. Intervention during the 24-hour treatment period was analyzed according to treatment group. Analyses were performed with R software, version 2023.06.1 (R Foundation), and SAS software, version 9.4 (SAS Institute). Additional details regarding interim analyses, analyses of processes of care and protocol adherence, subgroup analyses, and secondary analyses are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From October 26, 2021, through November 3, 2025, we identified 2080 eligible patients, of whom 1000 underwent randomization: 499 to the vasopressor group and 501 to the fluids group (Figs. S1 and S2). Informed consent was not provided for 37 patients (18 in the vasopressor group and 19 in the fluids group), which left an intention-to-treat population of 963 patients (481 in the vasopressor group and 482 in the fluids group). Three patients assigned to the fluids group were lost to follow-up for the primary outcome. The representativeness of the trial population is shown in Table S2.

Baseline characteristics appeared to be similar in the two groups (Table 1 and Table S3). The prerandomization median fluid volume was 1500 ml (interquartile range, 1000 to 1750) in the vasopressor group and 1500 ml (interquartile range, 1000 to 1850) in the fluids group. Treatment with vasopressors was initiated before randomization in 57 patients (11.9%) in the vasopressor group and 41 patients (8.5%) in the fluids group. The respiratory tract and urinary tract were the most common infection sites in both groups (Table 1). The number of patients who underwent a source-control procedure was 79 (16.4%) in the vasopressor group and 94 (19.5%) in the fluids group. Times to surgery appeared to be similar between the groups (Table S5).

INTERVENTION

Within 24 hours after randomization, the percentages of patients receiving a vasopressor infusion were 86.5% in the vasopressor group and 67.6% in the fluids group (difference, 18.9 percentage points; 95% confidence interval [CI], 13.3 to 24.5). The median time to vasopressor initiation was 0.4 hours (interquartile range, 0.2 to 0.9) and 1.4 hours (interquartile range, 0.4 to 3.1), respectively (difference, –1.0 hours (95% CI, –1.2 to –0.9) (Table 2). A total of 346 patients (71.9%) in the vasopressor group and 267 patients (55.4%) in the fluids group received a vasopressor infusion through a peripheral venous catheter in the first 24 hours (difference, 16.5 percentage points; 95% CI, 10.5 to 22.4).

The median fluid volume received in the first 6 hours after randomization in the vasopressor and fluids groups was 500 ml (interquartile range, 250 to 1000) in the vasopressor group and 1500 ml (interquartile range, 1000 to 2091) in the fluids group (difference, –1000 ml (95% CI, –1088 to –884) (Table 2 and Fig. S3). By 24 hours after randomization, 1140 ml (interquartile range, 500 to 2120) and 2248 ml (interquartile range, 1500 to 3332), respectively, had been administered (difference, –1108 ml; 95% CI, –1395 to –850). Cumulative fluid administration over the 24 hours after randomization is shown in Figure S3. Additional details regarding vasopressor and fluid delivery during the intervention period are provided in Table S6. Fluid balance across the first 7 days is shown in Figure S4. A total of 367 of 480 patients in the vasopressor group (76.5%) and 326 of 481 patients in the fluids group (67.8%) were admitted to the ICU (difference, 8.7 percentage points; 95% CI, 3.0 to 14.3). Patient disposition in the first 24 hours after randomization is shown in Figure S5. A total of 74 patients (15.4%) in the vasopressor group and 73 patients (15.1%) in the fluids group received invasive mechanical ventilation (relative risk, 1.02; 95% CI, 0.76 to 1.36). The time to first cessation of invasive ventilation appeared to be similar in the two groups (Table 3).

Protocol adherence was high, as shown in Tables S7 and S8. Among patients who survived at least 6 hours, the intervention was delivered

Table 1. Characteristics of the Patients and Therapies at Baseline.*

Characteristic or Therapy	Vasopressor Group (N=481)	Fluids Group (N=482)
Median age (IQR) — yr	68 (58–77)	69 (56–77)
Male sex — no. (%)	281 (58.4)	302 (62.7)
Median weight — kg†	79 (65–95)	78 (66–94)
Usual residence — no. (%)		
Home	465 (96.7)	452 (93.8)
Long-term care facility‡	16 (3.3)	30 (6.2)
Median Charlson Comorbidity Index score (IQR)§	1 (0–3)	1 (0–3)
Median APACHE II score (IQR)¶	18 (15–23)	18 (14–22)
Median modified SOFA score (IQR)‖	4 (3–6)	4 (3–6)
Median systolic blood pressure (IQR) — mm Hg	85 (79–92)	86 (80–91)
Median lactate level (IQR) — mmol/liter	3.3 (2.5–4.7)	3.2 (2.4–4.5)
Median total IV fluid administered (IQR)**		
Volume — ml	1500 (1000–1750)	1500 (1000–1850)
Volume by body weight — ml/kg	18 (13–23)	18 (13–23)
Invasive mechanical ventilation — no. (%)	3 (0.6)	2 (0.4)
Vasopressor infusion††		
Initiated before randomization — no. (%)	57 (11.9)	41 (8.5)
Median time from emergency department presentation to start of infusion (IQR) — hr	2.57 (1.66–4.01)	3.7 (2.12–5.63)
Median time from emergency department presentation to randomization (IQR) — hr	2.10 (1.30–3.20)	2.10 (1.30–3.40)
Median time from confirmation of inclusion criteria to randomization (IQR) — hr‡‡	0.30 (0.10–0.60)	0.30 (0.10–0.60)
Primary site of infection — no. (%)		
Pulmonary	144 (29.9)	156 (32.4)
Urinary tract	112 (23.3)	121 (25.1)
Intraabdominal	66 (13.7)	71 (14.7)
Skin and soft tissue	64 (13.3)	67 (13.9)
Primary bloodstream	11 (2.3)	5 (1.0)
Other§§	16 (3.3)	6 (1.2)
Unknown	68 (14.1)	56 (11.6)
Median time from emergency department presentation to administration of first dose of antimicrobial agent (IQR) — hr	0.97 (0.57–1.53)	0.85 (0.52–1.52)

* Percentages may not total 100 because of rounding. Baseline variables are data obtained closest to, but before, randomization. IQR denotes interquartile range, and IV intravenous.

† Body weight (actual, estimated, or documented) was available for 469 patients in the vasopressor group and 465 in the fluids group.

‡ Residence in a long-term care facility did not include independent living in a retirement village, hostel, or rest home or hospital-led care in the home.

§ Chronic coexisting conditions were defined with the use of the Charlson Comorbidity Index (scores measure the effect of the weighted values for coexisting medical conditions on mortality and range from 0 to 33, with higher scores indicating a greater burden of disease).

¶ Scores on the APACHE II (Acute Physiology and Chronic Health Evaluation II) scale range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. Scores were based on the worst recorded values within the 24 hours before randomization and were calculated to assess baseline equivalence.

‖ Scores on the Sequential Organ Failure Assessment (SOFA) scale range from 0 to 24, with higher scores indicating more severe organ dysfunction. The SOFA scores are modified with the use of the ratio of oxygen saturation as measured by pulse oximetry to the fraction of inspired oxygen for the respiratory component. Scores were based on the worst recorded values within the 24 hours before randomization and were calculated to assess baseline equivalence.

** Total fluids included intravenous boluses administered in the ambulance before arrival to the emergency department and between arrival at the emergency department and randomization. Boluses were 500 to 1000 ml administered within 60 minutes. Maintenance fluids and fluids for medication delivery and catheter flushes were excluded. The median total volume of intravenous fluid administered between the time of arrival at the emergency department and the time the inclusion criteria were met was the same in both groups — 1000 ml (IQR, 1000 to 1500).

†† Vasopressor infusions included one or more of the following at any dose for at least 30 minutes: norepinephrine, epinephrine, vasopressin, metaraminol, dopamine, or phenylephrine.

‡‡ Data were available for 480 patients in the vasopressor group and 479 patients in the fluids group.

§§ Other sites included bone, joint, and central nervous system.

for less than 6 hours in 27 of 475 patients (5.7%) in the vasopressor group and 31 of 476 patients (6.5%) in the fluids group. Six patients (1.2%) in the vasopressor group received a fluid bolus without an algorithm-guided indication, and 71 patients (14.8%) received a fluid bolus of more than 250 ml (Table S8). In the first hour after randomization, the vasopressor group received a median fluid volume of 185 ml (interquartile range, 0 to 500) and the fluids group received a median of 1000 ml (interquartile range, 500 to 1080) (difference, −800 ml; 95% CI, −930 to −670). A total of 12 patients (2.5%) in the fluids group did not receive a 500-ml bolus for hypotension or hypoperfusion. The between-group separation for receipt of fluids and vasopressors was stable over the duration of the recruitment period (Figs. S7, S8, and S9). The delivery of interventions appeared to be similar when analyses were stratified according to country (Figs. S10, S11, and S12). Temporal changes in physiological and laboratory variables appeared to be similar over the intervention period (Table S9 and Fig. S13).

PRIMARY OUTCOME

The median number of days alive and out of the hospital at day 90 was 76 days (interquartile range, 55 to 83) in the vasopressor group and 76 days (interquartile range, 55 to 82) in the fluids group (difference, 0.0 days; 95% CI, −2.7 to 2.7; P=1.00) (Table 3 and Fig. 2). Results appeared to be similar when patients who died within 90 days after randomization were assigned −1 day alive and out of the hospital (Table S10). Findings appeared to be similar with adjustment for country and prespecified baseline covariates. The effect of the intervention on days alive and out of the hospital at day 90 did not appear to differ meaningfully in any prespecified subgroup (Fig. 2).

SECONDARY AND TERTIARY OUTCOMES

Mortality at 90 days appeared to be similar in the two groups (relative risk of death in the vasopressor group, 1.14; 95% CI, 0.85 to 1.54) (Table 3). The hazard ratio for death by day 90 was 1.17 (95% CI, 0.85 to 1.62) (Fig. S14). Among patients receiving vasopressors, the median time to first cessation of vasopressors was 22.4 hours (95% CI, 9.5 to 42.2) in the vasopressor group and 30.1 hours (95% CI, 11.9 to 51.1) in the fluids group. For patients admitted to the ICU, the median time to first ICU discharge was 59.3 hours (95% CI, 35.3 to 94.2) and 69.0 hours (95% CI, 42.0 to 117.4), respectively. Other outcomes appeared to be similar in the two groups (Figs. S15 and S16).

SAFETY OUTCOMES

Few prespecified complications related to either trial intervention occurred; an exception was pulmonary edema, which was reported in 3 (0.6%) patients in the vasopressor group and 24 (5.0%) patients in the fluids group (relative risk, 0.12; 95% CI, 0.03 to 0.39; P<0.001) (Table S11). One adverse event related to asymptomatic hypertension occurred in the vasopressor group.

DISCUSSION

In this multicenter, randomized trial involving patients presenting to the emergency department with septic shock, hemodynamic resuscitation during the first 24 hours with restricted fluids and early vasopressors, as compared with more liberal fluids and later vasopressors, did not increase the number of days alive and out of the hospital from randomization to day 90. Subgroup analyses of treatment effects and key secondary outcomes, including mortality, appeared to be similar in the two groups.

Our findings are consistent with those in the CLOVERS trial, which showed no mortality benefit at hospital discharge with a 24-hour restricted fluid strategy for patients with sepsis and a systolic blood pressure of less than 100 mm Hg. Our trial enrolled patients that met the Sepsis-3 criteria for septic shock, which ensured inclusion of patients with a well-defined, clinically severe form of septic shock.[6,19] A major difference between our trial and others that evaluated restrictive fluid strategies in septic shock is that we enrolled patients in the emergency department before they had been administered intravenous fluid in the amount of 30 ml per kilogram, allowing us to generate practice-informing data regarding initial fluid resuscitation that has been recommended in guidelines without high-quality evidence.[3,8,20-23]

We achieved meaningful separation in vasopressor and fluid administration during the first 6 hours. Separation in fluid administration was sustained through the 24-hour period after randomization, although most fluid was administered in the initial 6 hours in both groups, consistent with fluid administration in other studies of early resuscitation in septic shock.[6,8,24] Despite separa-

Table 2. Fluid and Vasopressor Administration (24-Hour Intervention Period).

Variable	Vasopressor Group (N=481)	Fluids Group (N=482)	Difference (95% CI)*
Median volume of IV fluid administered (IQR) — ml†			
0 to 1 hr	185 (0 to 500)	1000 (500 to 1080)	−800 (−930 to −670)
0 to 6 hr	500 (250 to 1000)	1500 (1000 to 2091)	−1000 (−1088 to −884)
6 to 24 hr	480 (0 to 1100)	600 (0 to 1256)	−120 (−437 to 0)
0 to 24 hr	1140 (500 to 2120)	2248 (1500 to 3332)	−1108 (−1395 to −850)
Median volume of IV fluid administered (IQR) — ml/kg†			
0 to 1 hr	2 (0 to 6)	10 (5 to 16)	−9 (−10 to −7)
0 to 6 hr	7 (3 to 14)	20 (13 to 27)	−13 (−15 to −12)
6 to 24 hr	5 (0 to 14)	8 (0 to 17)	−3 (−5 to −1)
0 to 24 hr	14 (6 to 27)	29 (18 to 43)	−15 (−18 to −12)
Vasopressor initiation, 0 to 24 hr			
Patients — no. (%)‡	416 (86.5)	326 (67.6)	18.9 (13.3 to 24.5)
Median time to vasopressor initiation (IQR) — hr§	0.4 (0.2 to 0.9)	1.4 (0.4 to 3.1)	−1.0 (−1.2 to −0.9)
Vasopressor administration by peripheral venous catheter — no. (%)	346 (71.9)	267 (55.4)	16.5 (10.5 to 22.4)
Duration of vasopressor administration by peripheral venous catheter — hr	6.2 (3.4 to 14.9)	5.7 (3.0 to 18.7)	0.5 (−1.1 to 1.7)
Central venous catheter in situ — no. (%)¶	188 (39.1)	180 (37.3)	1.7 (−4.6 to 8.1)
Vasopressor infusion by central venous catheter — no. (%)	179 (37.2)	159 (33.0)	4.2 (−1.8 to 10.2)

* Differences are reported as differences in the medians for continuous variables and as percentage-point differences for percentages.
† Data regarding fluid administration were collected during the 24-hour intervention period unless a patient was transferred to a noncritical area of the hospital or to a nonparticipating hospital before completion of the period. Analyses of fluid volume per kilogram of body weight were restricted to patients with recorded body weight (469 patients in the vasopressor group and 465 in the fluids group). The interval from 0 to 1 hour represents the time from randomization to the end of the first full hour after randomization.
‡ Vasopressor infusion included one or more of the following agents at any dose for at least 30 minutes: norepinephrine, 244 of 385 patients (63.4%) in the vasopressor group and 207 of 342 (60.5%) in the fluids group; epinephrine, 17 of 362 (4.7%) and 25 of 333 (7.5%), respectively; vasopressin, 62 of 368 (16.8%) and 59 of 334 (17.7%); metaraminol, 128 of 371 (34.5%) and 113 of 338 (33.4%); and phenylephrine, 2 of 361 (0.6%) and 0 of 331.
§ Time to vasopressor initiation is reported for patients who received a vasopressor infusion (416 patients in the vasopressor group and 331 in the fluids group). Patients who received a vasopressor infusion before randomization were assigned 0 hours as the time of vasopressor initiation.
¶ Data shown are for central venous catheters or peripherally inserted central catheters.

tion across the suite of algorithm-guided interventions, patient outcomes in the two groups appeared to be similar.

Our pragmatic trial was conducted across various health care settings, and neither resuscitation targets nor specific measures of responsiveness to fluids were specified.[25] Rather, algorithm-guided therapies were individualized according to usual care, enabling generalizability of our findings to routine practice. Regular monitoring ensured sustained adherence to the intervention, including across geographic regions and over time.

Our trial had certain limitations. Owing to the nature of the intervention, treatment could not be administered in a blinded manner. The intervention was limited to the first 24 hours and did not control for variables during the subsequent hospitalization, including discharge decisions. However, such decisions occurred later under the care of clinicians who were generally unaware of the treatment assignment, and the potential for bias was probably minimal. Biased ascertainment of intervention-related adverse events was mitigated by a systematic and standardized approach to safety monitoring. However, pulmonary edema events in the fluids group may, in part, have been caused by reporting bias.

Several tertiary time-to-event outcomes, such

Table 3. Outcomes.

Outcome	Vasopressor Group (N=481)	Fluids Group (N=482)	Effect Estimate (95% CI)*
Primary outcome†			
Median no. of days alive and out of the hospital from randomization to day 90 (IQR)	76 (55 to 83)	76 (55 to 82)	0.0 (–2.7 to 2.7)
Days alive and out of the hospital to day 90, adjusted analysis‡	—	—	1.3 (–0.8 to 3.3)
Secondary outcomes			
Death by day 28 — no. (%)	62 (12.9)	48 (10.0)	1.29 (0.91 to 1.85)§
Death by day 90 — no./total no. (%)	79/481 (16.4)	69/479 (14.4)	1.14 (0.85 to 1.54)§
Time between randomization and death	—	—	1.17 (0.85 to 1.62)¶
Median no. of days alive and at home at day 90 (IQR)‖	76 (46 to 83)	76 (46 to 82)	0.8 (–1.9 to 3.5)**
No. of days free of organ support at day 28 (IQR)††‡‡			
Vasopressor support	27 (26 to 28)	27 (26 to 28)	–0.2 (–0.5 to –0.1)**
Invasive ventilation	28 (28 to 28)	28 (28 to 28)	0.6 (–0.1 to 1.4)**
Renal replacement therapy	28 (28 to 28)	28 (28 to 28)	0.2 (–0.5 to 0.9)**
Tertiary outcomes			
Death in an intensive care unit — no./total no. (%)	32/370 (8.6)	28/333 (8.4)	
Death in a hospital, censored at 90 days — no./total no. (%)	60 (12.5)	46 (9.5)	1.31 (0.91 to 1.88)§
Use of organ support — no. (%)††‡‡			
Vasopressor support	416 (86.5)	331 (68.7)	1.26 (1.18 to 1.35)§
Invasive ventilation	74 (15.4)	73 (15.1)	1.02 (0.76 to 1.37)§
Renal replacement therapy	30 (6.2)	25 (5.2)	1.20 (0.72 to 2.01)§
Time-to-event outcomes from randomization (IQR)§§			
First cessation of vasopressors — hr	22.4 (9.5 to 42.2)	30.1 (11.9 to 51.1)	1.25 (1.12 to 1.41)¶¶
First cessation of invasive ventilation — hr	45.4 (15.9 to 188.8)	67.9 (22.1 to 185.9)	1.14 (0.85 to 1.53)¶¶
First cessation of renal replacement therapy — hr	114.0 (45.2 to 274.0)	138.8 (80.5 to 302.3)	1.13 (0.69 to 1.87)¶¶
Time to emergency department discharge — hr	4.0 (2.4 to 6.5)	4.7 (2.9 to 8.2)	1.15 (0.99 to 1.34)¶¶
Time to intensive care unit discharge — hr	59.3 (35.3 to 94.2)	69.0 (42.0 to 117.4)	1.23 (1.06 to 1.43)¶¶
Time to hospital discharge — days	6.8 (3.7 to 12.9)	7.1 (4.1 to 13.9)	1.02 (0.89 to 1.18)¶¶

* Confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

† The number of days alive and out of the hospital at day 90 was defined as the number of days that the patient was not in an acute care hospital during the index hospitalization and did not have a subsequent overnight readmission to an acute care hospital. Patients who died on or before day 90 were assigned 0 days alive from the time of randomization to day 90. The analysis was performed with the use of a linear quantile mixed-effects regression model at the 0.5 quantile, with treatment group as a fixed effect and trial site as a random effect. Three patients were lost to follow-up for the primary outcome, and their data were used for analyses of days alive and out of the hospital at day 90 by means of multiple imputation under the assumption that data were missing at random. P=1.00 for the primary outcome.

‡ The adjusted analysis included the baseline covariates of country, APACHE II score, site of infection, and lactate level in the primary linear quantile mixed-effect model.

§ The effect estimate shown is the relative risk.

¶ The effect estimate shown is the hazard ratio for all time-to-event outcomes.

‖ Days alive and at home to day 90 was defined as a return to the preadmission usual place of residence, excluding days not spent in an acute care hospital during the index hospitalization, any subsequent short-term hospital overnight readmission, or admission to inpatient rehabilitation or a nursing home (unless the nursing home was the usual residence).

** The effect estimate shown is the median difference.

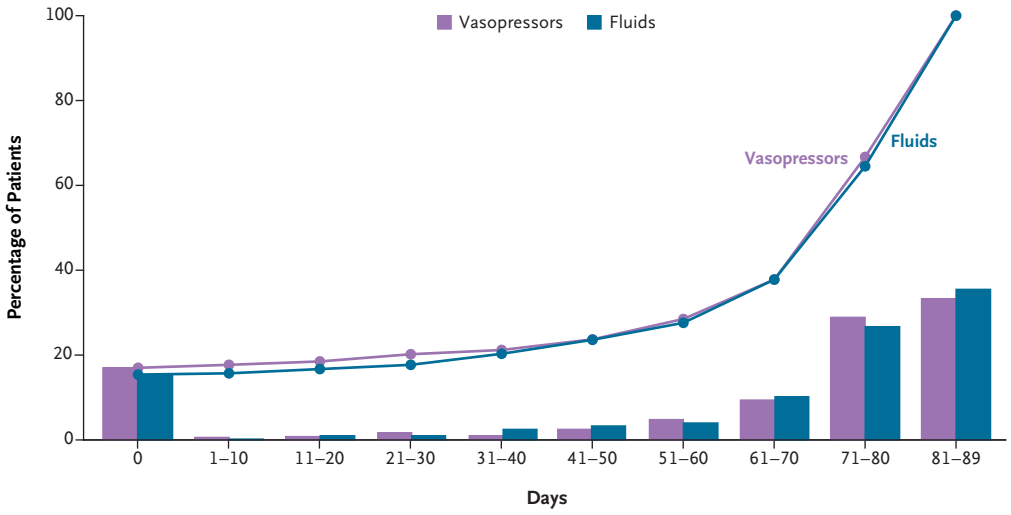
†† Receipt of organ support was recorded up to day 28 after randomization. Days alive and free of organ support were calculated from the time of randomization to day 28. Patients who died on or before day 28 were assigned 0 organ-support–free days. The number of organ-support–free days was defined as the time alive and without invasive mechanical ventilation, vasopressor support, or renal replacement therapy through day 28 after randomization, expressed in days.

‡‡ Vasopressor support refers to administration of a vasopressor at any time throughout the index hospital admission, from emergency department presentation until hospital discharge; the data shown include patients for whom vasopressors were first initiated after the 24-hour intervention period was completed.

§§ Incidence and time-to-event measures related to vasopressor administration and discharge from the emergency department or intensive care unit were influenced by group assignment during the intervention period and should be interpreted as process outcomes rather than direct measures of patient benefit.

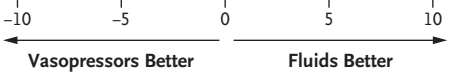
¶¶ The effect estimate shown is the cause-specific hazard ratio.

A Days Alive and out of the Hospital from Randomization to Day 90



B Subgroup Analyses

Subgroup	Vasopressors	Fluids	Median Difference (95% CI)
	no. of patients with event/total no.		
All patients	481/481	479/482	−0.00 (−2.67 to 2.67)
Age			
<65 yr	207/481	201/479	−0.95 (−3.81 to 1.91)
≥65 yr	274/481	278/479	1.49 (−2.09 to 5.00)
Sex			
Male	281/481	300/479	0.26 (−3.99 to 4.52)
Female	200/481	179/479	−1.00 (−4.02 to 4.00)
Lactate			
<3 mmol/liter	196/481	211/479	1.13 (−1.69 to 3.94)
≥3 mmol/liter	285/481	268/479	−2.00 (−6.88 to 1.63)
Apache II			
<15	119/481	144/479	2.61 (−1.03 to 6.25)
≥15	362/481	335/479	−1.06 (−5.07 to 1.92)
IV fluids before randomization			
<1500 ml	240/481	236/479	0.06 (−3.08 to 3.21)
≥1500 ml	241/481	243/479	0.00 (−3.30 to 3.45)
Source of sepsis			
Respiratory	144/481	154/479	−1.60 (−8.32 to 4.05)
Urinary	112/481	121/479	0.71 (−2.00 to 4.22)
Other	225/481	204/479	0.85 (−3.08 to 5.85)



as vasopressor cessation and discharge from the emergency department or ICU, were directly influenced by the intervention, with downstream processes partly determined by treatment strategy. We regard differences in these outcomes as descriptive measures of clinical management and delivery of a complex intervention rather than independent evidence of direct patient benefit. These differences did not translate into a difference in the primary outcome. Clinicians excluded a sizeable proportion of patients with a treatment limitation. Patients with preexisting conditions and fluid restriction (e.g., cardiac failure) and patients who had received more than 2000 ml of intravenous fluid before screening were also excluded, reducing generalizability. Treatment separation may have been attenuated because some patients did not receive the algorithm-guided

Figure 2 (facing page). Distribution of Days Alive and out of the Hospital to Day 90 and Subgroup Analyses for the Primary Outcome.

Panel A shows the distribution of days alive and out of the hospital from randomization to day 90 (the primary outcome) among patients in the vasopressor group or the fluids group. Patients who died before day 90 were considered to have had 0 days alive and out of the hospital at day 90. Points on the lines indicate the cumulative percentage of patients in each group for whom the primary outcome was ascertained at each time point. Panel B shows the median difference in days alive and out of the hospital to day 90 (vasopressor group vs. fluids group), with 95% confidence intervals overall and for prespecified subgroups. The overall estimate includes imputed values for the primary outcome (three patients were lost to follow-up), whereas subgroup analyses were performed without imputation. Square sizes are proportional to subgroup size and horizontal bars represent 95% confidence intervals. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores range from 0 to 71, with higher scores indicating greater severity of illness. Prerandomization fluid volume was dichotomized at the median volume. Confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

therapy or because exposure was less than 24 hours owing to transfer out of a critical care area.

As with any composite outcome, the choice of primary outcome reflects the combined influence of its components. In this trial, the individual-component outcomes did not appear to differ between the groups. The sample-size calculation was based on a number of days alive and out of the hospital at day 90 that had been derived from previous observational data and included an inflation factor to account for the non-normal distribution of the outcome events. The observed distribution of days alive and out of the hospital in our trial was consistent with assumptions that were used for the sample-size calculation. Finally, our findings may not be generalizable to low-income countries or health care settings with limited resources.

Among patients presenting to the emergency department with early septic shock, administration of restricted volumes of fluids and early vasopressors, as compared with greater volumes of fluids and later vasopressors, did not increase the days alive and out of the hospital from randomization to day 90.

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